CAPACITY OF ADENYLYL CYCLASE ISOFORMS TO GENERATE INTRACELLULAR SIGNALS IN RESPONSE TO MECHANICAL STIMULI. Peter A. Watson, John Krupinski, and Kathryn E. Giger. Weis Center for Research, Geisinger Clinic, Danville, PA 17822.

In perfused hearts, anabolic responses in response to pressure appear to be coupled to a stretch-induced accumulation of adenosine 3', 5' cyclic monophosphate (cAMP). Work in a simple cell model, hypotonic swelling of S49 mouse lymphoma cells, has delineated a probable signal transduction pathway responsible for cAMP accumulation following cell deformation. Acceleration of adenylyl cyclase (AC) activity occurs following cell deformation which apparently occurs independent of the actions of the guanine nucleotide-binding regulatory proteins (G-proteins) involved in hormonal regulation of cAMP synthesis. Mechanoresponsive AC activity is also influenced by the integrity of the actin cytoskeleton, implying a possible role for this structure in regulation of AC by mechanical forces.

Work in this laboratory and others has indicated that AC exists in multiple isoforms, with no particular subtype corresponding exclusively to mechanoresponsive cells and tissues. Work has been initiated involving expression of specific AC subtypes in 293 cells which lack endogenous mechanoresponsive AC activity to determine if mechanoresponsiveness is a conserved property within the AC family. Expression of the calmodulin-sensitive Type I AC imparts mechanoresponsive cAMP accumulation to 293 cells, which appears to occur independent of changes in intracellular calcium and calmodulin activity. In contrast, expression of the "olfactory-specific" Type III AC in 293 cells does not impart mechanoresponsive cAMP accumulation.